EFFECTS OF POSTEXTRASYSTOLIC POTENTIATION ON NORMAL AND FAILING HEARTS*

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INTRODUCTION

IT HAS BEEN KNOWN for about 80 years that the heart beat that follows an early extrasystole is stronger than the regular beat.[1] This phenomenon, which has been of interest to us for several years, we have studied on strips of heart muscle,[2] on the isovolumically contracting right ventricle,[3] and on the heart in failure.[4, 5] Important studies of this phenomenon in the isovolumically contracting ventricle also were reported some years ago by Katz and his co-workers.[6] The premature extrasystole that evokes the potentiation of the following contraction is itself mechanically ineffective in that in the intact heart it causes little or no demonstrable increase in intraventricular pressure. Recently Lopez, Edelist, and Katz[7, 8] suggested that the fact that the early extrasystole is mechanically ineffective might be utilized to control otherwise refractory tachycardias. They reasoned that if artificial electrical stimulation could be used to evoke a premature beat in every cycle, the electrical rate of the heart would be doubled in relation to its mechanical rate; the rate of mechanical contraction thus could be reduced to approximately one half the rate during tachycardia. Also, the heart would thus be shielded from endogenous extrasystoles by virtue of having two complete driven action potentials for each mechanical response. This ingenious suggestion has proved to be valid, and it has been further developed by Chardack and his associates,[9] who recognized the presence of postextrasystolic potentiation in their experiments. Braunwald and his co-workers[10, 11] subsequently published studies in

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which they too noticed this effect. They, however, stated that while what they observed is "a form of postextrasystolic potentiation" it "differs from the classical form of postextrasystolic potentiation."

Since we feel that the mechanical effects seen when extrasystoles are evoked early in each cycle are in every sense identical with those long known and carefully studied as postextrasystolic potentiation (PESP) we wish to present a review of that phenomenon here. Having done so, we shall go on to summarize and enlarge upon our studies of the beneficial effects of postextrasystolic potentiation in acute cardiac failure in experimental animals. Some of the results presented here are not new, and many of those that are new could have been predicted from a knowledge of the physiology of postextrasystolic potentiation. We have, however, repeated all crucial experiments within the context of the possible benefits of maintained postextrasystolic potentiation in acute cardiac failure. We have made this presentation as comprehensive as possible so that there will be less need for well-known facts about postextrasystolic potentiation to be rediscovered by possibly hazardous studies on the normal human heart.

If a series of regular contractions of an isolated papillary muscle is interrupted by a single extrasystole the first postextrasystolic contraction shows an increase in maximum force developed and an increase in the rate of contraction and relaxation.[2, 3, 5, 6, 10] Moreover, the change in contractility caused by the extrasystole persists for some time so that each of the next several contractions shows a gradual decrease in potentiation. It is easy to demonstrate that the extent to which the postextrasystolic contraction is potentiated depends primarily on the prematurity of the extrasystole. If the cycle length is sufficiently long to prevent the occurrence of dropped beats and to prevent the postextrasystolic contraction from being itself premature, then the records show that as the extrasystole is introduced progressively later after the driven contraction, the potentiation of the postextrasystolic beat is less and less marked. Obviously, if the cycle length is so short that the postextrasystolic contraction is premature, it may not show maximum potentiation. However, gradation in the degree of potentiation caused in this manner is due to the gradual recovery of contractility, or restitution;[12-14] evidence strongly indicates that potentiation is constant throughout the period of restitution and, in the absence of contractions, declines only slowly.

A variety of studies have shown that potentiation of the postextrasystolic contraction is not a result of the change in frequency of contraction, the presystolic fiber length, the duration of the active state or change in the characteristics of the action potential.[2] When postextrasystolic potentiation is induced in the isovolumic ventricle *in situ*[3, 6] the phenomena are essentially the same as those described for the isolated papillary muscle.

All of the changes caused by a single premature contraction are observed if the extrasystole is introduced in each cardiac cycle; however, in this case the potentiation builds to a maximum over several cycles and is considerably greater than that following the single extrasystole.[2, 5, 6] Potentiation increases the force of both the basic contractions and the extrasystoles. As in the case of the single extrasystole, the degree of potentiation depends on the prematurity of the extrasystole. The change in force of the potentiated beats is not the result of the doubling of rate since, even when the frequency of contraction is so high that force is diminished, introduction of an extrasystole in each cycle causes a marked increase in the rate of contraction and relaxation and in the peak force of contraction. When the paired stimuli are interrupted, the first beat that is not followed by an extrasystole is the last postextrasystolic contraction, and it initiates a gradual decline in potentiation that usually requires five or more beats for completion.

Obviously, as in the case of single extrasystoles, the degree of potentiation that results when pairs of stimuli are used to maintain postextrasystolic potentiation depends in large measure on the cycle length. If the cycle length is short enough so that contractility is not fully restored between each pair of contractions, potentiation is less marked. Variations in the cycle length of the basic contractions and in the degree of prematurity of the extrasystole thus can cause infinite variation in the degree to which the force of contraction is altered.

Methods

Since a variety of experimental preparations and techniques have been used in these studies of PESP, the description of each will be brief. In some instances, additional details of technique are included below under *Results*.

In situ *hearts.* Animals were anesthetized by intravenous injection of pentobarbital sodium, 28 to 30 mg./kg. Ventilation with room air was provided through an endotracheal tube by a Palmer pump. For experiments on intact animals, stimuli were applied to the heart either through electrodes that had been chronically implanted on the epicardial surfaces of the right atrium and right or left ventricle some time before the experiment, or through fine stainless steel wires passed through the chest wall and implanted in the ventricular myocardium by the method described by Ross.[15] For experiments on the exposed heart, the chest was opened by a median sternotomy. Electrodes similar to those used for chronic implantation were attached to the epicardium by subepicardial sutures. Stimuli were provided by Tektronix wave form and pulse generators or Grass stimulators and were delivered to the heart through stimulus isolation units. Pulse duration was 2 msec. and stimulus strength was adjusted to a value that never was greater than twice threshold. The site of application of the stimulus and pattern of stimulation in various experiments are described below.

Pressures were recorded through polyethylene catheters using Statham transducers. In experiments on intact animals, intraventricular pressures were recorded from the right and/or left ventricles by passing the catheter tip through the tricuspid and aortic valves respectively. In experiments on exposed hearts, short catheters were introduced directly into the ventricles through the walls of the chambers and fixed in position by purse-string sutures. In some experiments the rate of change of pressure was demonstrated by electronic differentiation. Records were obtained by means of an eight-channel Electronics for Medicine recorder.

Several other procedures were employed in studies of the *in situ* heart. In some experiments the resistance to outflow from the left ventricle was periodically increased for an interval of several seconds by constriction of the aorta at a point just distal to the left subclavian artery or just above the coronary ostia. In others, constriction of the pulmonary artery was employed to increase resistance to right ventricular ejection. Acute failure of the right ventricle was induced by maintained partial constriction of the pulmonary artery and administration of a beta-adrenergic blocking agent, pronethalol, in doses of 2 to 10 mg./kg. The criteria employed to demonstrate the presence of failure are described below under *Results.*

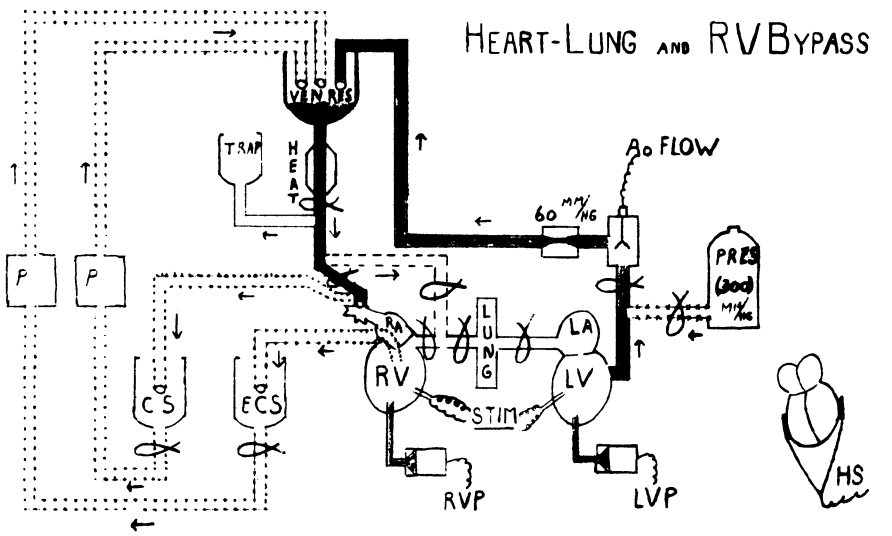

Fig. 1. Diagram of the experimental arrangement for both the heart-lung preparation and the right heart bypass. *RVP* and *LVP:* right and left ventricular pressure. *Ao Flow:* aortic flowmeter. *CS:* coronary sinus drainage. *P:* pumps. *ECS:* extracoronary sinus drainage. *HS:* heart size.

In some experiments the right ventricle was isolated from the circulation by means of the circuits shown in Figure 1 to provide a chamber that contracted isovolumically. After ligation of the azygos vein, blood from the superior and inferior venae cavae (not shown in Figure 1) was diverted to one reservoir that permitted measurement of systemic blood flow. From this reservoir blood was pumped to a constant-level reservoir connected to a cannula inserted in the common pulmonary artery just distal to an occlusive ligature. Blood temperature was controlled by a heated water jacket. Blood from the right atrium was diverted to another reservoir that permitted measurement of coronary sinus outflow. A catheter inserted in the right ventricle was used either to collect and measure coronary blood flow into the lumen of this chamber, to inject known amounts of blood, or to record intraventricular pressure. In most of these experiments the tricuspid valves remained competent. This was demonstrated by a constant end-diastolic pressure, at any fixed ventricular volume, for a period of many beats. For some experiments, this same procedure for right ventricular bypass was employed on the heart-lung preparation described below.

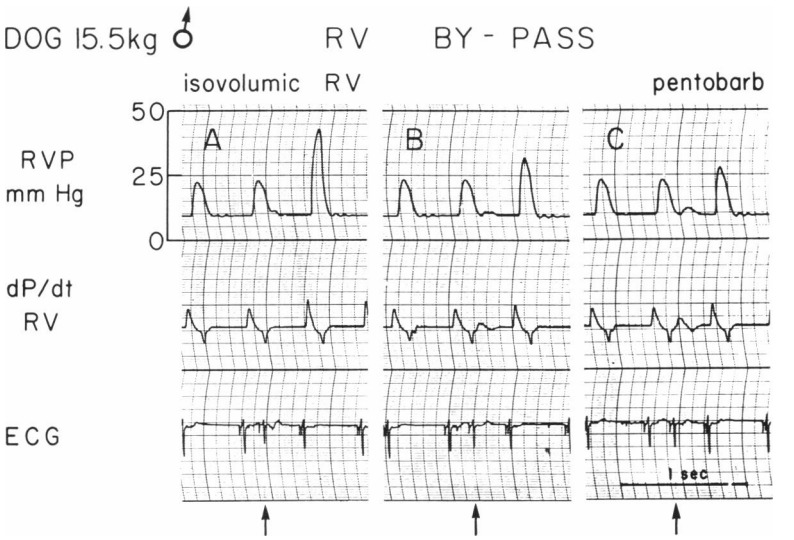

Fig. 2. The effect of a single premature stimulus on the pressure of the isovolumic ventricle at an early (*A*) and two later intervals (*B*, *C*).

Heart-lung preparations. Heart-lung preparations (HLP) were made using dogs anesthetized by intravenous injection of pentobarbital sodium, 30 mg./kg. Additional blood was obtained from dogs lightly anesthetized with pentobarbital and given heparin sodium, 5 mg./kg. The HLP and associated circuits are shown in Figure 1. In general, the techniques used to stimulate and record from the HLP were similar to those described above. In addition, the following procedures were carried out. Aortic blood flow was recorded continuously by means of a Shipley-Wilson flowmeter inserted between the aortic orifice and the Starling resistance. The flowmeter was directly calibrated during each determination by diverting the aortic flow into a graduated cylinder. Pressure in the Starling resistance under control conditions was set at 60 mm.Hg. Changes in blood content of the HLP were quantitated by noting changes in the content of the venous reservoir. In some experiments heart size was roughly quantitated by means of a recording caliper placed across the ventricles. Procedures employed to evaluate the competence of the HLP and to induce failure are described below under *Results*. When direct measurement of coronary drainage into the right atrium and ventricle was desired, the right ventricular bypass, as shown above, was combined with the HLP.

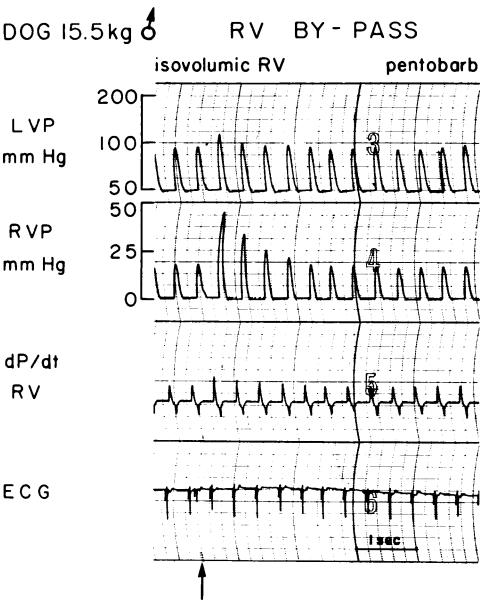

Fig. 3. The effect of a single premature stimulus on the pressure of the isovolumic ventricle. Note the persistence of the potentiation through several succeeding beats.

Results

Effect of a single premature beat in the isovolumic ventricle. If a single premature beat is introduced into an otherwise regular rhythm the beat immediately following the premature beat is altered in several important ways, all of which are illustrated in Figure 2. The maximum systolic pressure developed within the ventricle is increased. The rate of development of pressure is increased, as may be seen not only from inspection of the intraventricular pressure pulse but also from examining the time derivative of the pressure change. Not only does the rate of contraction increase but the rate of relaxation also increases. Since both contraction and relaxation occur more swiftly, the total duration of systole is reduced.

Another feature of the postextrasystolic potentiation induced by a single premature beat is the fact that the amount of postextrasystolic potentiation depends on the prematurity of the extrasystole. Figure 2C shows the effect of an extrasystole that occurs so late in the cycle that it causes a clear rise in intraventricular pressure. The immediately following beat shows postextrasystolic potentiation of moderate degree,

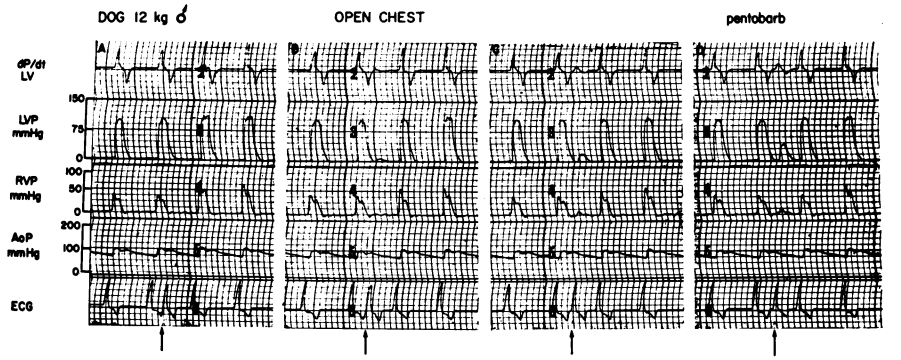

Fig. 4. The effect of a single premature stimulus delivered at various delays on the pressure developed by the intact *in situ* heart. The traces, from above down, are dp/dt of the left ventricle; left intraventricular pressure; right intraventricular pressure; aortic pressure and lead II electrocardiogram. Arrows indicate the time of the premature stimulus.

with moderate changes in peak intraventricular pressure, rate of development of tension, rate of relaxation, and duration of systole. Figure 2*B* shows the effect of an extrasystole that falls at a time when its mechanical effect is manifested only by a slurring in the relaxation phase of the previous normal beat. All of the phenomena of post-extrasystolic potentiation are shown to a more marked degree than in Figure 2*C*. Figure 2*A* shows the effect of the earliest extrasystole that can be evoked with the stimulus employed in this experiment. All of the effects of PESP are seen to be increased over their values in Figure 2*B*. By increasing the strength and duration of the stimulus it may be made to excite slightly earlier but the increase in PESP will not exceed 5 per cent, and the stimulus required to obtain this slightly earlier excitation and slightly increased PESP will be a stimulus far more hazardous from the point of view of evoking fibrillation.

The results reported in the two previous paragraphs refer only to the effect of a premature stimulus on the beat that immediately follows it. The effect of a single extrasystole actually persists for several beats in diminishing degree. Figure 3 shows this fact. For each of six or seven beats following the extrasystole there is an increase above control values not only of the peak systolic pressure but also of the rate of contraction and the rate of relaxation, and a decrease in the duration of systole as compared with the control value. Each successive beat shows these changes to a lesser degree than does the beat that preceded it.

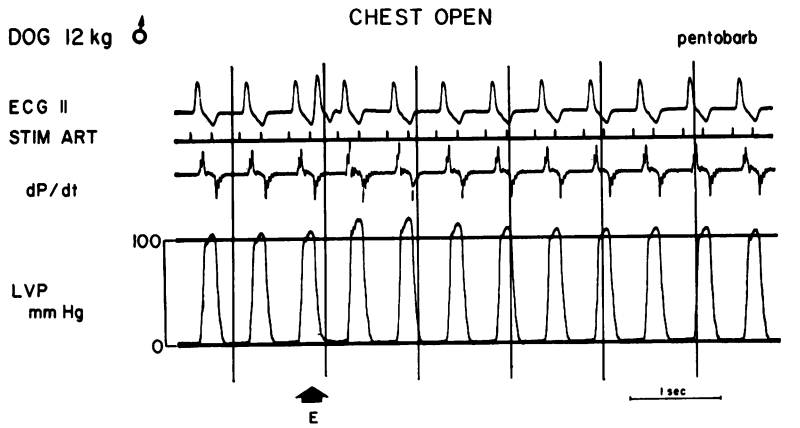

Fig. 5. The persistence of the effect of a single premature stimulus on the pressures developed by the intact *in situ* heart. All tracings as in Figure 4.

Effect of a single premature beat on the in situ *heart.* Figure 4 shows the effect of a single premature beat on the intact *in situ* heart. It will be seen that all of the phenomena of postextrasystolic potentiation are revealed in this preparation and that they are graded according to the prematurity of the extrasystole. In particular, as the prematurity of the extrasystole is increased the magnitude of the premature mechanical response diminishes, the increment in left ventricular pressure increases, and the rates of contraction and relaxation increase. As in the case of the ventricle that contracts under isovolumic conditions, if the next regular contraction occurs too soon after the premature beat, incomplete restitution may cause some decrease in the force developed by the ventricle. Also, in the intact heart the mechanical response to a late extrasystole may cause some reduction in filling of the ventricle. At fairly rapid ventricular rates both of these factors act in concert to weaken the first postextrasystolic beat; as a result, maximum potentiation is not observed and, often, the second postextrasystolic beat shows the greatest enhancement of contractility.

Figure 5 shows the persistence and gradual decay of PESP in a series of beats following the single extrasystole. These records are precisely similar to those shown above for the isovolumically contracting ventricle, but it is important to note that the apparent effects of PESP are present to a lesser degree in every case. There is a lesser in-

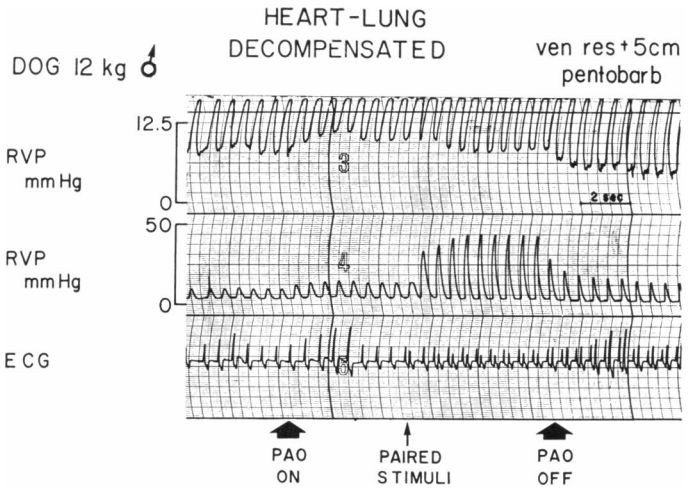

Fig. 6. The effects of maintained PESP on the isovolumic right ventricle in a heart-lung preparation. From above down, right intraventricular pressure at high sensitivity, right intraventricular pressure at low sensitivity, and lead II electrocardiogram. At the arrow *PAO* the pulmonary artery was occluded and, simultaneously, venous inflow was stopped and aortic resistance was dropped to zero. Note the modest increase in right ventricular pressure after pulmonary artery occlusion and the marked increase in systolic pressure and decrease in end-diastolic pressure after paired stimulation is initiated.

crease in peak intraventricular pressure, a lesser rise in the rate of contraction and the rate of relaxation, and a lessened shortening of the duration of systole. These differences are explicable by reference to two facts. First, the valves are permitted to open, which lessens the load on the heart and prevents the maximum rise in intraventricular pressure. Second, in the intact animal reflex adjustments in vasomotor tone may cause a compensatory vasodilatation. This further masks the apparent effect of PESP. One thing this experiment shows is that the intact, *in situ*, unfailed heart is possibly the least suitable preparation for the study of PESP.

Effect of maintained PESP on the isovolumic ventricle. In this section we examine the effects of maintained postextrasystolic potentiation, i.e. the effects of a rhythm in which every mechanically effective beat is preceded by a very premature mechanically ineffective extrasystole. Figure 6 shows a few control beats followed by the onset of maintained PESP. In this situation the amount of potentiation increases during each of the first three to five beats before reaching a steady state. The steady state of PESP is maintained at an unaltered level for

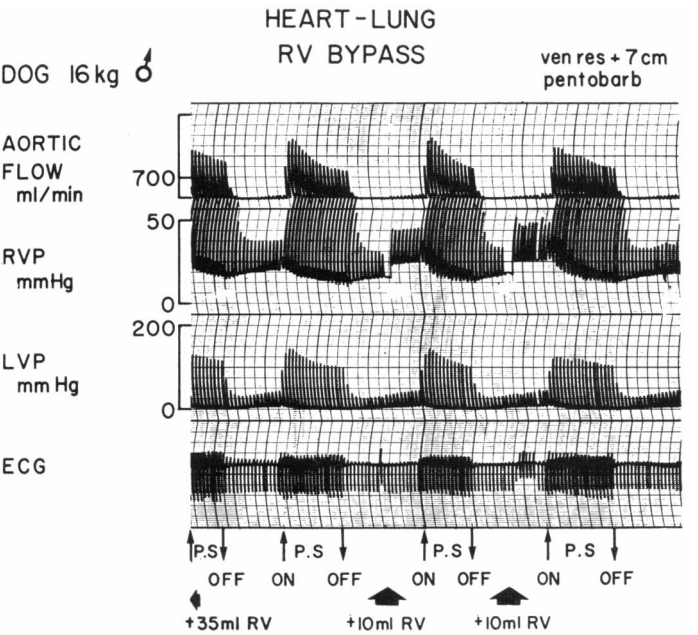

Fig. 7. Heart-lung preparation with right ventricular bypass. From above down, aortic flow, right intraventricular pressure, left intraventricular pressure, and lead II. Prior to the beginning of the record the isovolumic right ventricle was distended with 35 ml. of blood. Paired stimuli were applied between the arrows. Note the decrease in end-diastolic pressure in the right ventricle during paired stimulation and the increase that follows the cessation of paired stimulation. At the large arrows increments of 10 ml. of blood were injected into the right ventricle and the stimulation sequence repeated.

a long period (up to many hours). Each of the effects of PESP shows a buildup to a steady state level: rise in peak systolic pressure, rise in rate of contraction, and relaxation and shortening of the duration of systole. When PESP is discontinued there is a gradual decay of the effect: the decay is less rapid, i.e., the effects of PESP persist longer than in the heart that has received a single extrasystole.

Maintained PESP often causes a slight fall in end-diastolic pressure, even in the apparently unfailed isovolumically contracting ventricle. This is seen in Figure 6, although to a small degree. Since the ventricle is assumed neither to fill nor to empty, this observation is at first glance difficult to explain. Investigation has shown that this fall in end-diastolic pressure is the result of a probably very important effect of PESP: an increase in diastolic compliance of the ventricle. Figure 7 shows the appreciable increases in end-diastolic pressure that occurs

when the decompensated bypassed right ventricle is distended by the injection of blood through the pressure catheter. Following each increment of ventricular volume, maintained PESP is induced and causes a progressive decrease in end-diastolic pressure as well as other expected effects on contraction. Immediately on resumption of regular rhythm, end-diastolic pressure increases until PESP is initiated once again.

A possible criticism of these experiments is that there may be some regurgitation of blood through the atrioventricular valves and that this regurgitation might be more marked during the potentiated systoles. However, several facts suggest that such regurgitation, even if it occurs, cannot be the sole explanation for the decrease in end-diastolic pressure during PESP. In the experiment shown in Figure 7, the initial increment in ventricular volume was 35 ml.; this was followed by two injections of 10 ml. each. After each 10-ml. increment in volume, end-diastolic pressure in the right ventricle did not fall during an interval of approximately 5 sec. This observation shows that the tricuspid valve was reasonably competent.

The increase in end-diastolic pressure following the cessation of PESP also suggests that a true increase in compliance occurs during PESP and slowly vanishes when PESP is stopped. The increase in end-diastolic pressure following cessation of PESP might, however, be thought to result from luminal coronary flow. If the increase were, in fact, the result of coronary flow into the cavity of the right ventricle one would expect even greater changes in end-diastolic pressure *during* PESP when left ventricle and coronary artery pressure are much increased. Moreover, the record of aortic flow showed that, at least during the first four to five beats of each period of normal rhythm when diastolic pressure increased most rapidly, there was no aortic flow. One thus may assume that the aortic valves remained closed during each contraction of the left ventricle and that coronary flow was negligible. It seems reasonable to conclude, therefore, that although there may have been some small change in the volume of blood in the right ventricle during each test period, the large changes in end-diastolic pressure result in the main from changes in diastolic compliance.

Effect of maintained PESP on the intact in situ *ventricle.* When maintained PESP is induced in the intact *in situ* heart all of the expected effects may be noted: rise in intraventricular systolic pressure, change in rate of contraction and relaxation, and shortening of systole

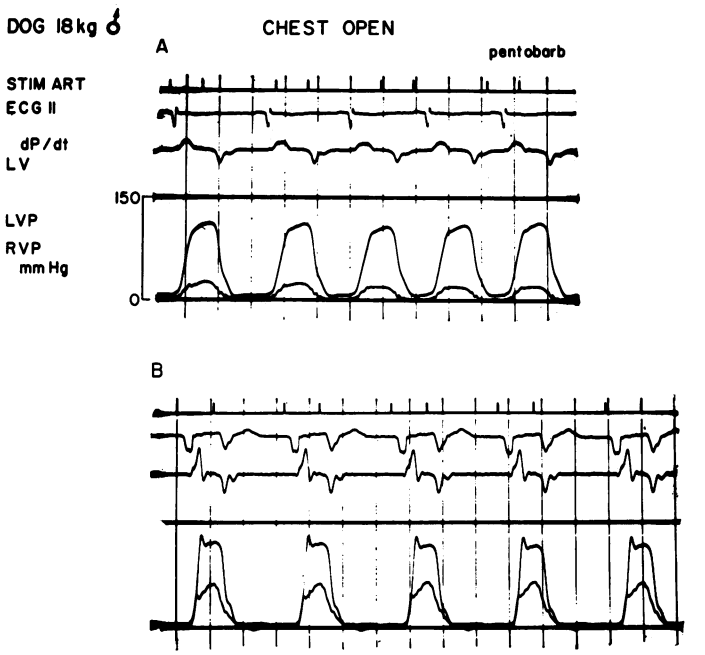

Fig. 8. The effect of maintained PESP on the intact *in situ* heart. From above down, stimulus artifact, lead II electrocardiogram, dp/dt of the left ventricle, left intraventricular pressure, and right intraventricular pressure. *A* shows records during ventricular drive and *B* shows records during maintained PESP. See text for discussion.

(Figure 8). In addition, a variable slight decrease in end-diastolic pressure is often seen even when there is no other evidence of failure. All of these changes are seen to a less marked degree in the intact *in situ* ventricle than in the isovolumic ventricle. It was suggested in the section on the effect of a single extrasystole that this difference can be attributed in part to the fact that the valves open and permit ejection of blood during systole and, perhaps in part, to the role of compensatory reflex vasodilatation.

The role of the opening of the valves may easily be demonstrated by temporary occlusion of the aorta proximal to the brachiocephalic arteries. Under this condition, though the valves open, they open only at a much higher pressure, and the ventricle contracts against a high and relatively fixed resistance. In such an experiment the ventricle continues to fill during diastole by virtue of influx of blood from the atrium but since stroke volume is reduced, end-diastolic volume and pressure increase progressively. Figure 9 shows the progressive rise in

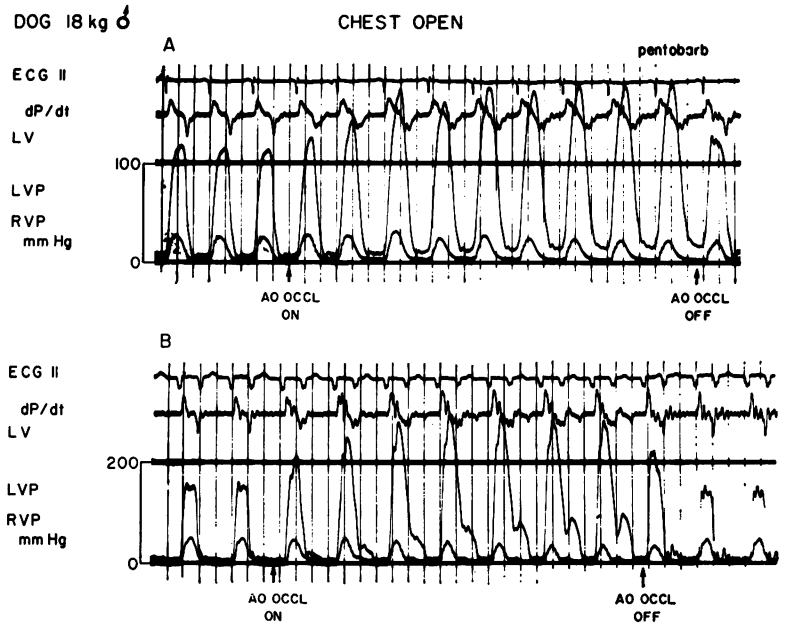

Fig. 9. *In situ* heart. Records from above down show lead II electrocardiogram, dp/dt of the left ventricle, left intraventricular pressure, right intraventricular pressure. Note that the sensitivity of the left ventricular pressure trace is changed in *B*. The record shows control beats followed by aortic occlusion in *A* during regular rhythm; in *B* during maintained PESP. See text for discussion.

peak-systolic pressure and end-diastolic pressure which follows such an occlusion of the aorta, and Figure 9*B* shows the effect of such occlusion during maintained PESP. When the aorta is occluded the rise in peak-systolic pressure associated with PESP is very much greater than the rise in peak-systolic pressure during normal rhythm. This shows that the augmentation of contractility caused by PESP may be very great in the normal heart, provided conditions are such that it can manifest itself.

This experiment also provides another demonstration of the effect of PESP in increasing diastolic compliance. When the aorta is clamped during a normal rhythm, end-diastolic pressure rises with each successive beat. When the aorta is clamped during maintained PESP, there is a lesser increase in end-diastolic pressure even though the peak-systolic pressure is greatly increased and the heart continues to fill from the atrium. Although part of the diminution in end-diastolic pressure might result from greater ejection, much of it is thought to

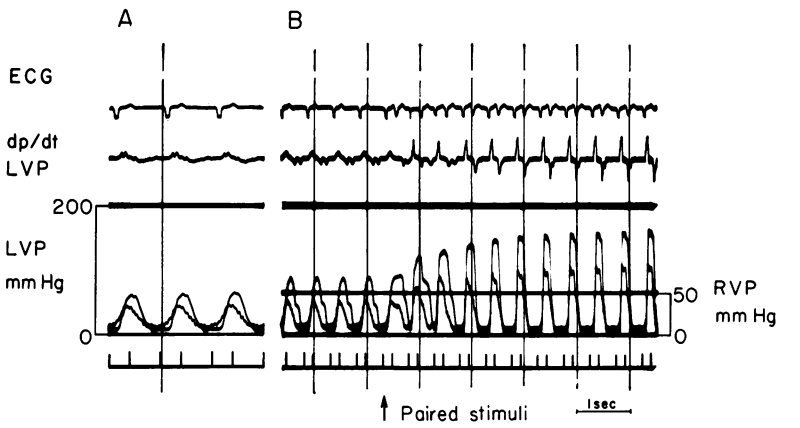

Fig. 10. *In situ* heart. From above down, lead II electrocardiogram, dp/dt of the left ventricle, left intraventricular pressure, and right intraventricular pressure. *A* shows control records. In *B* the initial four beats show the effect of an infusion of norepinephrine and the potentiation induced in the following beats by paired-pulse stimulation.

result from increased compliance.

If our conclusions about the effect of PESP on diastolic compliance of the ventricle are correct, one can not assume that data obtained at similar values of end-diastolic pressure during regular rhythm and PESP represent measurements made at similar end-diastolic fiber lengths. If the data could be plotted in terms of fiber length, the displacement of any curve showing the effect of PESP thus might be less marked. Although conclusions concerning the effects of PESP on contractility are valid it may be difficult to give quantitative expression to such effects.

The effect of reflex adjustments in vasomotor tone may be investigated by infusing a dose of norepinephrine sufficient to overwhelm the peripheral effectors of these reflexes. Such on infusion maintains a high and relatively fixed degree of peripheral vasoconstriction that is virtually independent of the play of reflexes upon the arterioles. Figure 10 shows the effect of PESP on an animal subjected to such an infusion. The dose was set at the highest level that would not evoke frequent extrasystoles. When maintained PESP was induced there was a further marked increase in peak systolic pressure, a further increase in the rate of rise of contractile force and rate of relaxation, and a shortening of systole. This once more shows that the effects of PESP on the intact ventricle may be demonstrated far more readily if the

outflow resistance is high. It also shows that PESP exerts a marked additional inotropic effect even in the presence of the inotropic effects of a rather large concentration of norepinephrine.

A further illustration of the role of the outflow resistance may be found by comparing the effect of PESP on the intraventricular pressures of the right and left (Figure 8) ventricles. In an intact *in situ* heart with all vasomotor reflexes intact, the induction of maintained PESP causes the pressures developed during systole to rise considerably more in relation to control levels in the right ventricle than in the left. Since there is some increase of cardiac output at constant rate in these experiments, and since duration of systole and ejection time are abbreviated during maintained PESP, ejection velocity must be increased. The impedance of the pulmonary bed is known to be a function of ejection velocity, increasing markedly as ejection velocity increases. Impedance in the systemic circuit increases much less markedly as a function of ejection velocity. Thus the relatively greater increase in right ventricualr systolic pressure is a further indication that the effects of maintained PESP on blood pressure in the intact animal depend in considerable part on the outflow resistance.

Effect of PESP on the acutely failed heart. Effects of PESP on hearts in acute experimental failure have been studied using a variety of preparations. A detailed description of the experimental results will be given here for the HLP; similar results obtained for the failed *in situ* heart are presented in the section on the effect of PESP during beta-adrenergic blockade.

Competence of the HLP was evaluated by either or both of two methods; with the first, the height of the venous reservoir was elevated by known increments (usually 10 cm.) and the change in left and right ventricular pressures, heart size, and aortic flow were measured; with the second, aortic resistance was increased and the change in the same variables measured. The results obtained during such a competency test performed on an unfailed HLP are shown in Figure 11*A*. With progressive elevation of the venous reservoir to heights 10 and 20 cm. above the control level there was a progressive increase in aortic flow, peak left and right ventricular systolic pressure, and only a moderate increase in right ventricular end-diastolic pressure and heart size. Data from this and other experiments are presented in Table I. Figure 11*B* shows the effects of a similar competency test performed

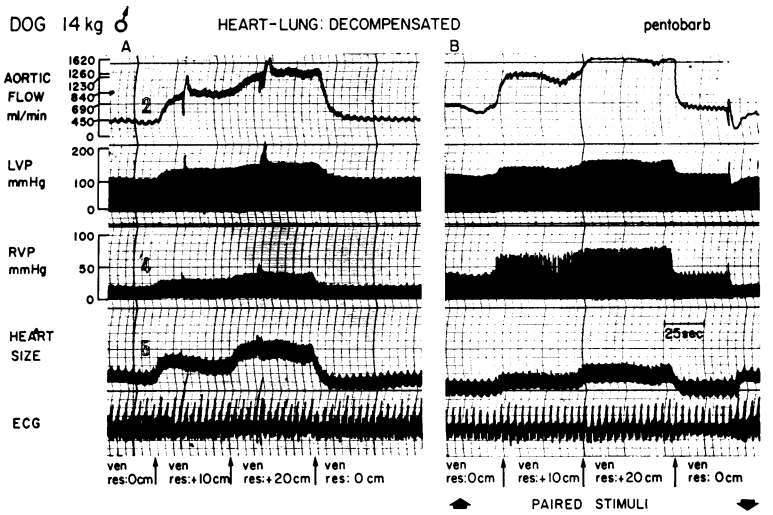

Fig. 11A Fig. 11B

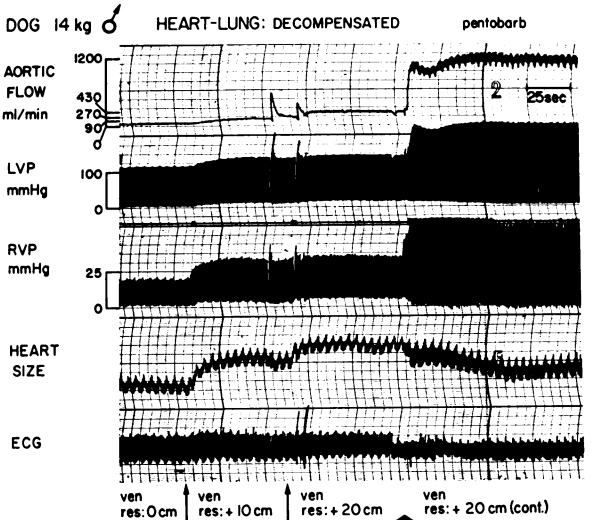

Fig. 11C

Fig. 11. Heart-lung preparation. From above down, aortic flow, left intraventricular pressure, right intraventricular pressure, heart size, and lead II electrocardiogram. The records in *A* show competency tests performed during regular rhythm prior to decompensation. Those in *B* show competency tests immediately afterwards during maintained PESP. The records in *C* show decompensation during regular rhythm and a marked improvement in performance during PESP. See text for detailed discussion.

TABLE I

Preparation	Venous Res.	Rt. vent. pressure Before PESP	Rt. vent. pressure After PESP	L. vent. pressure Before PESP	L. vent. pressure After PESP	Cardiac output Before PESP	Cardiac output After PESP
1	+20	88/18	100/0	60/12	156/1	150	1,200
2	+20	68/18	104/8	96/18	168/11	300	1,050
3	+10	8/6	25/4	45/15	130/0	180	690
4	+10	6/0	24/0	65/20	175/10	150	1,200
5	+20	30/5	50/-2	145/15	220/5	270	1,200
6	+30	30/20	45/10	65/20	165/12	150	1,400
7	+10	12/6	20/4	70/8	120/2	450	950

Effect of postextrasystolic potentiation on right and left intraventricular pressures (in mm. Hg) and on cardiac output (in ml./min.) in hearts in acute failure. These values were obtained from heart-lung preparations and the height of the venous reservoir is shown in centimeters of blood above normal central venous pressure.

from the results described in previous sections, PESP caused some moderate improvement of performance at all levels of the venous reservoir (see also Table I). After control data of this sort had been obtained repeatedly, the HLP was stressed either by maintaining the venous reservoir at a level of 20 cm. above the control, by maintaining the aortic resistance at 100 to 120 mm. Hg, or by a combination of these two procedures.

The presence of failure was evaluated in terms of the change in aortic flow, the change in end-diastolic and peak-systolic pressures in the left ventricle, and the change in heart size recorded both at normal and elevated levels of the venous reservoir. An increase in end-diastolic pressure and heart size and a decrease in aortic flow and peak-systolic pressure were recorded after development of failure. Also, there was a marked decrease in aortic flow when the aortic resistance was elevated. Finally, under such conditions, elevation of the venous reservoir caused little increase in aortic flow, but did result in a marked elevation of end-diastolic pressures and increase in heart size. The records obtained from such a preparation are shown in Figure 11C. In the presence of an aortic resistance of 100 mm. Hg, aortic flow was only 60 ml./min. at a normal venous pressure. Moreover, elevation of the venous reservoir caused a marked elevation of end-diastolic pressure in both ven-

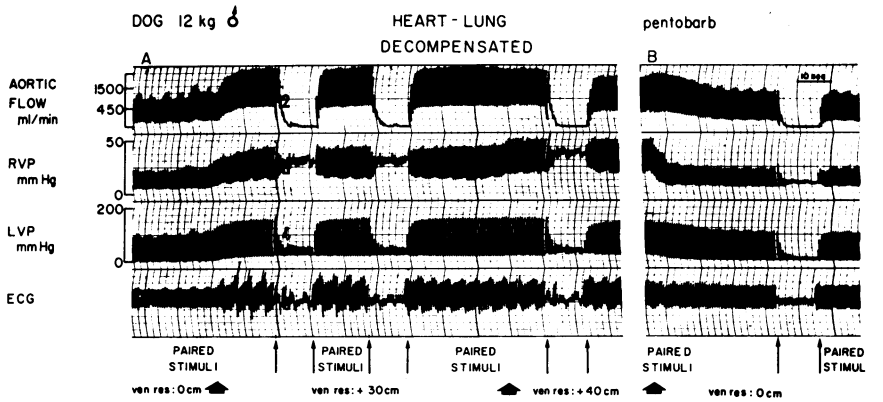

Fig. 12. Decompensated heart-lung preparation. From above down, aortic flow, right intraventricular pressure, left intraventricular pressure, and lead II electrocardiogram. Before the first large arrow the venous reservoir pressure was at the control height. Between the first and second large arrows the venous reservoir was elevated 30 cm. Between the second and third large arrows the venous reservoir was elevated 40 cm. After the third large arrow the venous reservoir was returned to the control level. At each filling pressure paired-pulse stimulation was interrupted briefly to demonstrate the resulting dramatic changes in pressures and flow.

tricles and a similarly marked increase in heart size without restoring aortic flow even to the normal control value. With aortic resistance maintained at 100 mm. Hg and the venous reservoir kept at a level 20 cm. above the control, PESP was initiated. Within a few beats aortic flow increased to 1,200 ml./min. Simultaneously there was a significantly reduction in end-diastolic pressure in both ventricles, a reduction in heart size, and an increase both in the peak-systolic pressure and maximum rate of development of pressure in the right and left ventricle. The improvement in performance was maintained—as long as the application of paired stimuli was continued—for periods of 30 to 60 minutes. After longer times the inevitable deterioration of the HLP resulted in progressive decompensation. If PESP was interrupted briefly after development of acute failure, pressures and flow rapidly deteriorated; on resumption of PESP, performance improved once again. Another striking example of the effects of PESP on the failed HLP is shown in Figure 12.

One additional variable was studied in the failed HLP. This was the relationship between the prematurity of the extrasystole and the change in aortic flow. As might be expected from the studies of pressure changes in normal hearts that resulted from variations in pre-

TABLE II

Preparation	*Heart rate*	*Delay in msec.*	*LVP mm. Hg*	*Aortic flow ml./min.*
1	102	260	85/6	600
		240	105/3	720
		230	125/2	840
2	138	170	85/5	720
		160	90/3	840
		150	97/3	980
3	102	170	102/3	558
		180	102/3	558
		190	95/4	546
		210	92/5	522
		220	92/5	492
		230	90/6	468
		250	90/6	468
		164	102/3	558

The effect of the position of the premature stimulus on cardiac output (aortic flow in ml./min.) and left ventricular pressure (in mm. Hg). Delay is given in milliseconds. Each of the above three studies was done on a heart-lung preparation with a right heart bypass; there was slight to moderate failure present in each case.

maturity of the extrasystole, during acute experimental failure the cardiac output, as well as the systolic and diastolic pressures, were dependent on the prematurity of the mechanically ineffective contraction. It thus was possible to cause graded changes in output by varying the interval between the pairs of stimuli. Examples of the dependence of aortic flow on prematurity of the extrasystole are shown in Table II.

The problems of long-sustained PESP and of the effect of stopping PESP may be briefly mentioned here. In various experiments we have found that PESP may be maintained for over 24 hours without any apparent diminution in its effectiveness. Moreover, if no adventitious deterioration in the state of the dog or of its heart has intervened, such dogs may be taken off PESP with return to normal cardiac output. In addition, it has been found that periods of PESP lasting up to several hours are not followed by any diminution of cardiac output when the PESP is stopped (Donald Singer and Gerald Galst, personal communication). We have observed, however, a striking fall in blood

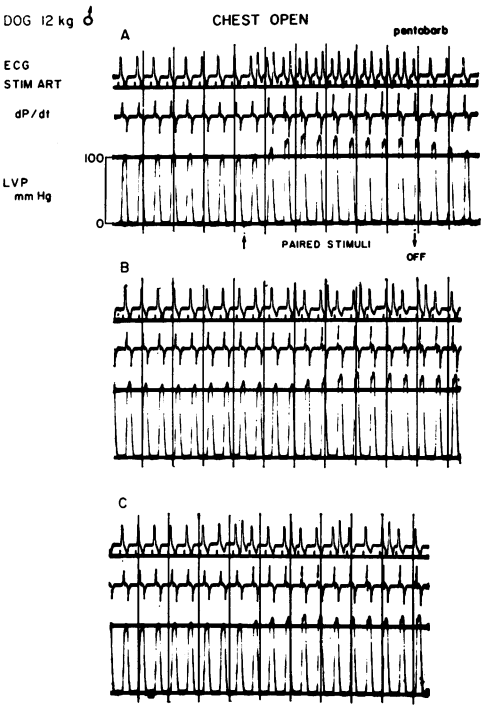

Fig. 13. Intact *in situ* heart. From above down. Lead II electrocardiogram, stimulus artifact, dp/dt of the left ventricle, and left ventricular pressure. In *A* paired stimulation is initiated between the arrows. In *B* the extrasystole occurs in every other cycle. In *C* the extrasystole occurs in every third cycle. Note the gradation in pressure and rate of contraction.

pressure immediately following cessation of PESP in the intact dog. This fall seems to be the direct result of the compensatory vasodilatation that has occurred during the rise in intraventricular pressure induced by PESP, and it does not reflect a fall in cardiac output attributable to the preceding period of PESP.

It is possible, nevertheless, that after prolonged PESP the heart may not immediately return to its ordinary state. For this reason we have investigated two methods by which the amount of PESP may be reduced in a gradual fashion. The first of these methods is based upon the fact that if the premature beat falls later in the cycle the amount of potentiation is lessened. Table II, referred to previously, shows the results of increasing the delay of the extrasystole in 10-msec. intervals. It will be seen that all important indices of cardiac function change in smooth fashion and that the later the extra stimulus falls the less is

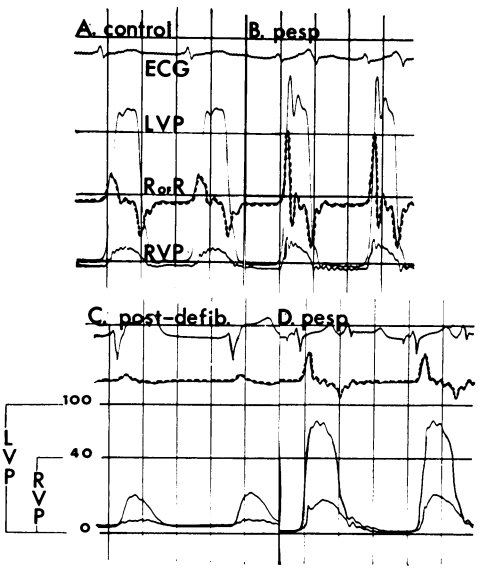

Fig. 14. Records obtained from an anesthetized dog with open chest under control conditions (*above*) and after treatment with pronethalol (*below*). The second set of records was obtained after spontaneous ventricular fibrillation and electrical defibrillation and represents a heart in terminal condition. Each set of records shows, from top down, a lead II ECG, left ventricular pressure (*LVP*), the first derivative of the left ventricular pressure (*R of R*), and right ventricular pressure (*RVP*). Tracings of the rate of change of ventricular pressure have been emphasized by dashed lines to prevent confusion with the pressure tracing. Time lines are at intervals of 200 msec. Pressure calibration, in mm. Hg is shown for right and left ventricles. Note the marked change in rate of development of left ventricular pressure accompanying the postextrasystolic potentiation (pesp) and the relatively greater potentiation obtained when the paired stimuli are applied to the compromised heart. See text from discussion. (From Cranefield *et al.*[5])

the PESP. Such a technique has the disadvantage that the extrasystole may become mechanically ineffective. This may be avoided by another technique that is shown in Figure 13. Here PESP is induced by applying a premature stimulus in every cycle, in every other cycle, and in every third or fourth cycle. This reduction in the frequency of application of premature stimuli causes a graded reduction in the amount of PESP induced. It is striking to note, in Figure 13, that the application of an extra stimulus during every other beat produced almost as much potentiation as did the application of a premature stimulus during every beat. The dropping of stimuli from the pattern of premature beats clearly offers an elegant method of weaning the heart from PESP, should such weaning be necessary, and offers an equally elegant method of controlling the "amount" of potentiation during maintained PESP.

Effects of PESP during beta-adrenergic blockade. Our studies of the effects of PESP on acute failure of the *in situ* heart have been reported elsewhere in some detail[5] and will be summarized only briefly at this time. Failure was induced, as described above under *Methods*, by partial constriction of the pulmonary artery and administration of pronethalol, a potent beta-adrenergic blocking agent. The presence of acute failure was judged by the occurrence of the following: a marked increase in end-diastolic pressure in the right ventricle and a marked decrease in systolic pressure in the same chamber, similar changes of lesser magnitude in the left ventricular pressures, and a marked increase in heart size. These changes developed slowly and, without PESP, led to death in all instances. The dramatic improvement caused by PESP is shown in Figure 14. The decrease in heart size and end-diastolic pressure and increase in right and left ventricular systolic pressure were maintained for the duration of the period of paired stimulation, even in the presence of maintained constriction of the pulmonary artery and continued administration of supplemental doses of pronethalol. When paired stimulation was interrupted, the heart rapidly returned to the failed state. Resumption of paired stimulation caused an immediate improvement. After development of acute failure there was a continued deterioration in the absence of PESP even when the pulmonary artery constriction was removed and additional pronethalol withheld. Conversely, under the same conditions, maintained PESP caused restoration of a circulatory status sufficiently normal to permit survival of the animal.

Effect of PESP on pulmonary edema. In the course of studying the effect of PESP on acute failure in the heart-lung preparation we have several times noted that when end-diastolic pressures were very high the dogs showed frank pulmonary edema as evidenced by bloody froth in the tracheal cannula. When PESP was initiated the end-diastolic pressure in both ventricles fell, the peak-systolic pressure in both ventricles rose, the cardiac output rose, and the pulmonary edema disappeared. The disappearance of pulmonary edema is simply one more piece of evidence in support of the statement that PESP can reverse acute cardiac failure. It is instructive, however, to note that the edema vanishes in the face of a marked rise in systolic pressure in the right ventricle and pulmonary artery. The fact is that pulmonary edema results from increases in pressure in the venous end of the

capillaries of the pulmonary circuit and is associated with high end-diastolic pressures in the left ventricle rather than with high mean pressures in the pulmonary artery.

Effect of random spontaneous extrasystoles. A premature beat need not be induced by the experimenter in order for it to cause postextrasystolic potentiation. A single premature beat of spontaneous origin will affect the heart in exactly the same way as if it were induced artificially. This can be a great inconvenience if frequent extrasystoles occur in the course of a study of PESP, but is of considerable clinical interest. Many published illustrations show the effect of spontaneous premature beats on intraventricular pressure pulses and on the rate of change of contraction and relaxation. As in the case of artificial PESP, it will be seen that potentiation follows a premature beat and that potentiation is greater if the prematurity of the beat is greater.

Effect of PESP on the heart after defibrillation. We have repeatedly observed hearts that have fibrillated and that have been defibrillated with difficulty after a prolonged delay. Such hearts commonly show prolonged and irregular QRS complexes and very poor mechanical performance. We have found that such hearts may be restored to excellent mechanical function by the application of PESP. We have noted at least a dozen cases in which the state of the heart was so bad that the experiment would automatically have been ended: in all of these cases the application of PESP restored the function of the ventricle to a virtually normal level and permitted the experiment to be carried on for many hours. It should be emphasized that in such experiments PESP was turned off as early as 15 min. after it was applied and that the heart then functioned normally. PESP thus is remarkably effective in the specific form of acute heart failure that follows upon an "unsuccessful" defibrillation, i.e., a defibrillation in which fibrillation is abolished, normal rhythm is established, but mechanical function is all but absent.

Effect of PESP in hemorrhagic shock. Preliminary experiments, to be reported in greater detail elsewhere, have shown that if dogs are placed in shock by the controlled bleeding technique of Wiggers and are kept at a shock level for some time, transfusion of the lost blood back into the animal does not lead to survival. If, however, PESP is applied to the heart the animal does recover from its state of shock and soon reaches a level of cardiac function sufficient to permit survival

without PESP. Thus, as we have indicated elsewhere,[5] the use of PESP may reverse the decline in cardiac performance that causes shock to become "irreversible."

Discussion

Postextrasystolic potentiation has been shown to exert the following effects on the contraction of cardiac muscle:

1) It increases the maximal force of contraction during systole.

2) It increases the rate of development of tension.

3) It often increases the rate of relaxation.

4) As a result of effects 2 and 3 it may decrease the duration of systole.

5) It increases diastolic compliance. All of these five effects can be demonstrated in isovolumically contracting ventricles, in the intact *in situ* ventricle and in the failed ventricle. In general, however, the effects are least marked in the normal heart *in situ* and are revealed most clearly in the ventricle contracting against a heavy resistive load or in the failed ventricle. Additional effects that can be seen in any heart, under appropriate conditions, but that are most vividly seen in the failed heart are:

6) A fall in end-diastolic pressure.

7) A marked increase in cardiac output.

8) An increase in coronary arterial flow (see Bartelstone *et al.* elsewhere in these proceedings).

9) A decrease in the size of the heart. These four effects may be briefly summarized by stating that postextrasystolic potentiation exerts a rapidly acting, sustained, and powerful positive inotropic effect on the ventricular myocardium.

Nature of the potentiation. It has been shown by various earlier studies that postextrasystolic potentiation occurs independently of any change in diastolic interval or filling. Potentiation of contraction is invariably seen at the earliest moment at which it can be seen, namely during the first contraction following the premature beat. Braunwald *et al.*[10, 11] place considerable emphasis on their observation that potentiation is seen only after the "second pair of stimuli" and not after the "first pair." However, in their terminology a pair of stimuli is made up of the stimulus giving rise to the driven beat plus the following stimulus, which gives rise to the premature beat. For the "first pair of

stimuli," thus defined, to induce potentiation, the premature beat would have to enhance the contraction of the contraction that precedes it. In the work of Braunwald *et al.* the first contraction following the extrasystole is in fact potentiated. If one wishes to speak of "pairs of stimuli" the logical pairing, from the point of view of postextrasystolic potentiation, is the pair made up of the stimulus that evokes the premature beat plus the stimulus that evokes the following driven beat. Braunwald *et al.* make a similar remark concerning the disappearance of PESP after the cessation of paired stimulation: they assert that PESP remains maximal after the "last pair of stimuli." Here again, of course, the fact is that PESP remains maximal as long as the driven beat is preceded by a premature beat. Potentiation begins to wane the moment a beat occurs that was not preceded by a premature beat. Although Braunwald *et al.* correctly interpret their observation as indicating that the phenomenon in question is postextrasystolic potentiation, we find their nomenclature for "pairs of stimuli" inherently confusing.

Braunwald *et al.* also note[10, 11] that the improvement in contractile force seen in their experiments "differs from the classical forms of postextrasystolic potentiation in two respects. First, when the time interval between the stimuli is carefully adjusted, the augmentation may occur without a discrete second mechanical event. Second, in the investigation presented herein, not only did the potentiation occur after a single extrasystole, as in most previous experiments, but it was found to be sustained as long as the appropriately timed, paired stimuli were applied to the ventricle." Both of these statements concerning peculiarities of PESP are erroneous. Many previous investigators have shown potentiation following extrasystoles that are virtually mechanically ineffective. That maintained premature stimulation of the heart produces maintained potentiation also is well known.[2, 3, 5, 6]

We cannot enter into a detailed discussion of how potentiation comes about because we do not know how it comes about. It seems most unlikely to us that PESP is the result of the release of catecholamines from the ventricle or from the sympathetic nerves in the ventricle as has been suggested as a possibility by Braunwald *et al.*[10, 11] As those authors point out themselves and as we also have observed,[5] PESP may be demonstrated in the reserpinized dog and in the presence of an enormous dose of beta-blocking agents such as nethalide. Moreover, the electrical stimulus is not one that would in any way be expected to

release appreciable quantities of amines from the heart or from its nerves. In addition, paired pulse stimulation can potentiate in the presence of the enhancement of contractility induced by very large doses of norepinephrine. Since PESP can act in the catecholamine-depleted dog, in the dog blocked by beta-blockers, and in the presence of nearly maximal catecholamine-induced inotropy, it seems unlikely that it acts by releasing catecholamines. In our opinion the most plausible explanation advanced thus far is that of F. Kavaler (personal communication) who has extensive evidence linking the potentiation to effects on Ca influx. For another approach to the explanation of PESP the reader is referred to the recent paper of Bonnet Seoane.[16]

As we have mentioned above, the evidence suggesting that increase in diastolic compliance accompanies postextrasystolic potentiation is striking. To what extent the enhanced force of contraction and the increased compliance may be causally related and to what extent they are independent manifestations of some more basic change we cannot say. It is known that an elevation of Ca^{++} increases both force of contraction and diastolic compliance.[17]

Induction of PESP. The technique of double pulse stimulation has already received clinical use in attempts to control refractory tachycardias, and its effect on acute heart failure is under active clinical investigation. The matter of the safest way in which to induce double pulse stimulation is therefore of considerable importance. We feel confident that the chief hazard connected with induction of PESP is that of accidentally causing ventricular fibrillation, and we feel that the danger of ventricular fibrillation may be reduced virtually to zero if proper methods are used. We have outlined the methods elsewhere[5] but once again we give a brief summary:

1) If a catheter electrode is used it is essential that it be of the type that can make and sustain firm contact with the myocardium. In our opinion transthoracic plunge electrodes[15, 18] are probably quicker to use for this purpose and, in the long run, safer than transvenous catheter electrodes.

2) All appropriate precautions against adventitious grounding must be taken.

3) Most important of all, the duration and strength of the stimulus must not be excessive.

The risk of fibrillation comes about in one of two ways: either a

hazardous stimulus may fall in the vulnerable period of a regular beat during the induction of double pulse stimulation, or a hazardous stimulus may fall in the vulnerable period of a spontaneous escape beat during maintained PESP. Both of these risks can be avoided or minimized simply by avoiding the use of a stimulus capable of causing fibrillation. A stimulus 2 msec. long and in strength no greater than twice diastolic threshold is exceedingly unlikely to cause fibrillation or multiple extrasystoles even if it falls directly in the vulnerable period. The stronger the stimulus is, and the longer it is, the more unlikely it is to cause fibrillation, should it fall in the vulnerable period. We have always obtained 95 per cent of the maximum possible potentiation with a stimulus of the strength and duration described and do not feel that there is any need for a longer or stronger stimulus. Studies of diseased human hearts may show that repetitive responses or fibrillating may be caused even if these precautions are observed. However, if such observations are based on stimulation through catheters, the evaluation of stimulus strength may be in error.

Site of origin of the mechanically effective beat. There are two ways in which maintained postextrasystolic potentiation may be induced: either the mechanically effective beat can be permitted to be of atrial origin or both the mechanically effective beat and the premature beat can be of ventricular origin. (In general, the premature beat cannot be of atrial origin because an atrial beat often cannot reach the ventricle early enough to cause good postextrasystolic potentiation.) There is one advantage to using an effective beat of atrial origin: it will have the additional mechanical effectiveness of the more nearly simultaneous activation of the ventricle that results from spread through the conducting system. In general, however, we feel that the advantages of having both stimuli delivered to the ventricle are very great. In particular we feel that this gives more complete control of the rhythm of the heart. It avoids, for example, the possible complications of spontaneous atrial extras triggering extra premature beats. Also it gives a more secure protection against an unexpected supraventricular arrhythmia to have both beats result from driving the ventricle.

One additional comment should be included at this point, although its subject probably is common knowledge. In the case of a person with complete heart block and a low idioventricular rate, the introduction of an extrasystole at any time during or after the T wave is likely to

initiate repetitive activity. For this reason, paired stimulation should be employed only after single driving stimuli have increased the ventricular rate to a safe level. For the same reason, use of extra stimuli coupled to the intrinsic QRS complex should not be attempted.

Potentiation following spontaneous extrasystoles. The fact that random spontaneous premature beats cause postextrasystolic potentiation is of course fully expected. The irregularly irregular rhythm of atrial fibrillation provides an interesting example of the effect of random premature beats on the force of ventricular contraction. The extreme irregularity of the size of the pressure pulse (and the accompanying pulse deficit) may result not only from the presence of contraction of less than normal strength but also from such contractions inducing postextrasystolic potentiation. The pulse irregularity in atrial fibrillation has many causes, among which are the presence of beats of diminished force (premature beats); the variable filling interval; and the presence of postextrasystolic potentiation. However, atrial premature beats seldom reach the ventricle early enough to cause marked potentiation. Another example may be found in the effect of bigeminy induced by digitalis toxicity. It has long been known that certain patients seem to be clinically improved when they are digitalized to toxic levels and show a sustained bigeminy. It seems very probable that such patients are in fact benefiting from maintained postextrasystolic potentiation. Among the many other examples of this phenomenon that may be seen in the clinic, we mention only one, namely palpitation. The beat that is subjectively experienced as an extrasystole is, of course, the postextrasystolic beat. Its increased force of contraction (which permits it to be subjectively recognized) may result in part from increased diastolic filling; it also certainly results in part from postextrasystolic potentiation. Indeed, if there is no prolongation of diastole, the increased contraction force must result solely from postextrasystolic potentiation.

The prevention of arrhythmias. The initial reports on paired pulse stimulation emphasize its value in slowing the heart. It should be pointed out that this is only a specific application and that paired pulse stimulation can be used perfectly well to prevent or control arrhythmias of any kind. The mere fact that twice as much as usual of the cycle is occupied by electrical activity means that ectopic beats will be in large measure suppressed. In particular, it is possible that recurrence of arrhythmia following a myocardial infarction can be largely suppressed

by the use of paired pulse stimulation.

Maintained paired pulse stimulation without potentiation. The force of the mechanically effective beat is a strict function of the interval that elapses between the premature electrical event and the onset of the effective beat. In fact, if the mechanically effective beat follows too soon after the premature beat, its force of contraction will be less than normal. Thus it is possible to adjust the heart rate and the position of the premature beat so that the force of the mechanically effective beat is less than, equal to, or greater than the force of a normal beat. This fact may be of importance in clinical situations in which the antiarrhythmic effect of paired pulse stimulation is desired but where it is felt that an increased force of contraction is undesirable. Reports of detailed investigations of this effect will appear elsewhere.

Indications for therapeutic investigations. The use of paired pulse stimulation for the treatment of refractory tachycardia is fairly well established on a trial basis. There is no doubt that it can slow the effective mechanical rate in a reasonably safe manner. It remains to be seen whether, or under what circumstances, it may prove to be the treatment of choice. It has been shown, at any rate, that paired pulse stimulation can be applied to the human heart with safety. When such stimulation of the heart is undertaken, postextrasystolic potentiation usually results. The question then arises: Is postextrasystolic potentiation as such a potentially useful therapeutic technique?

As we have indicated previously, we believe that the inotropic effect of postextrasystolic potentiation is of potential benefit in the treatment of acute cardiac failure. We also believe that it may be of value in certain forms of chronic cardiac falure, but for this assumption we have no direct evidence from animal experimentation. Our experiments on dogs clearly indicate that postextrasystolic potentiation can reverse all of the signs of acute heart failure, provided that the outflow resistance is reasonable and the venous return is adequate. By a reasonable outflow resistance we mean one which is not excessively low; if peripheral resistance is excessively low it must be raised by pressor agents. The adequacy of venous return is an obvious prerequisite; no inotropic agent can increase cardiac output beyond the limit set by venous return.

We have previously stated that the following conditions warrant the use of this technique: 1) there must be evidence of inadequate cardiac output; 2) central venous pressure must be high; 3) in the case

of shock, blood volume must be shown to be normal or above normal; and 4) the over-all situation must be sufficiently grave to warrant the investigative use of this technique. Among the various conditions in which we feel that the technique is of potential benefit there is one in which it shows particular promise and in which it may assuredly be tried without chance of harming the patient: that is after a defibrillation or resuscitation from cardiac arrest in which electrical activity is present but mechanical activity is inadequate to sustain life. We have repeatedly induced normal cardiac function under exactly these circumstances in dogs by simply inducing paired pulse stimulation. Indeed, accidental fibrillation complicated by prolonged and difficult defibrillation is no longer a serious problem when it interrupts an experiment. Animals whose hearts are so mechanically ineffective that they would assuredly have died (and we have about 14 years' experience with defibrillation in animal experiments) are readily restored to normal function by paired pulse stimulation.

Braunwald *et al.*[11] have noted that they found it difficult or impossible "to wean dogs with particularly poor left ventricular function off paired electrical stimulation" and they remark that this observation is one that "might point to a limitation of the clinical effectiveness of the method." While we have seen the same thing, we have more often seen dogs tided over a period of myocardial malfunction that would otherwise have been rapidly fatal. Moreover, what Braunwald *et al.* appear to say is that they have seen dogs that would assuredly have been dead were they not maintained by postextrasystolic potentiation, since they could not be "weaned" from it. That postextrasystolic potentiation kept those dogs alive is, it seems to us, a tremendous argument in favor of its clinical effectiveness, especially in situations in which a few hours or a few days may provide the time needed for either therapy or natural recovery to take effect. The difficulty of "weaning" patients with chronic congestive heart failure from digitalis is not exactly an argument against the clinical effectiveness of digitalis. That the abrupt cessation of maintained postextrasystolic potentiation results in a transient fall in cardiac output may be true but there is no need ever to discontinue it abruptly. Alternate premature beats may be dropped from the cycle (as we have described elsewhere), the premature beat may be caused to fall a little later in the cycle, or the potentiation may be turned on and off, weaning the heart from its effects gradually.

A condition analogous to that of the heart after resuscitation is seen in the heart that has reasonably normal excitability and electrical activity but greatly diminished mechanical activity following open-heart surgery. We believe that postextrasystolic potentiation may well be beneficial in such circumstances but must add a note of warning: patients subjected to cardiac surgery for the correction of long-standing defects may well have abnormal myocardial status and they may well be massively digitalized. We know of a patient in whom, during and after cardiac surgery, the induction of postextrasystolic potentiation was difficult or impossible because the heart responded to a very early extra stimulus only with a long latency (John Lister, personal communication). This may be the result of the diseased state of the myocardium or it may be the effect of rather heavy digitalization on the specialized conducting system. Nevertheless the technique clearly warrants further investigation in such cases because, if mechanical activity cannot be restored to a reasonable level, death inevitably ensues.

Another area of presumably great importance is to be found in patients in "irreversible shock." These are patients in whom restoration of blood volume has failed to reverse shock and in whom cardiac ouput is low and central venous pressure is high. Not uncommonly such patients have been transfused to the point where impending or actual hypervolumia and impending pulmonary edema forbid further transfusion; moreover, they are commonly maintained on pressor agents. In spite of this, urinary output falls, central venous pressure mounts, cardiac output falls, and death ensues. Such patients present a hemodynamic picture identical with that seen in the dog heart-lung preparations that we have studied, and there is every reason to suppose that they would respond similarly. It might be emphasized that many of these patients, and most postresuscitation patients, may well have had fully normal hearts prior to the onset of whatever event caused their acute cardiac failure: such patients might well be tided over by the temporary use of the powerful inotropic effect of postextrasystolic potentiation.

A particular form of irreversible shock that is common and grave is shock supervening upon myocardial infarction. When true and frank shock complicates myocardial infarction the prognosis is very nearly nil. It is well recognized that the use of vasopressor agents does not substantially improve the prognosis under such conditions. It is our belief that a patient who develops frank shock following myocardial infarction

and in whom norepinephrine is effective only in large doses, and who cannot be "weaned" from norepinephrine may very properly be treated by postextrasystolic potentiation. Such patients are in fact suffering from acute heart failure. They have low cardiac output and high central venous pressures (indeed they may develop pulmonary edema). The hazards of paired pulse stimulation are not trivial in such patients. There may be a risk of aggravating arrhythmias and there may be some risk secondary to the increase in intraventricular pressure. But both of these risks are already assumed when norepinephrine is administered. Moreover, the presence of two complete action potentials for each mechanically effective beat may well protect the heart against runaway tachycardias. Thus we feel that there are strong arguments for using this technique in certain cases of shock following myocardial infarction.

A further possibility for prudent investigation is the patient in chronic cardiac failure in whom temporary improvement of cardiac function is urgently needed (e.g. because of an intercurrent illness or because life-saving surgery is contraindicated by the cardiac status). We have no laboratory experience with the effects of postextrasystolic potentiation in chronic cardiac failure (in which full digitalization may be presumed). Nevertheless, we feel that in the circumstances mentioned above its cautious employment may be indicated.

Here we must raise two questions related to the safety of the technique. The first concerns the effect of postextrasystolic potentiation upon the oxygen demands of the myocardium. A certain amount of information is available on this point: it has been found that when a given heart is subjected to paired pulse stimulation it uses more oxygen than otherwise. This is natural and reasonable since it is being made to do more work.

The important clinical question is, however, quite different. If a failed heart is restored to competency by postextrasystolic potentiation, does it then use more oxygen than it would were it restored to competency by some other means? And even if it does, is the coronary flow improved so that any extra demand for oxygen can be met? These questions do not have simple or presently available answers. In relation to the effects of PESP on oxygen consumption, two factors should be considered in addition to that just mentioned. First, studies of mammalian skeletal muscle[18] have shown that the extra heat liberation associated with a fixed increment of work is greater if the velocity of

shortening is increased. Second, it has been shown[19] that if the rate of contraction and relaxation of an isolated feline papillary muscle are decreased, but presystolic and systolic tension remain constant, the oxygen consumption per beat is increased. Since PESP increases both the rate of contraction and relaxation, the cost of such contractions in terms of oxygen consumption may well be less than one would predict on the basis of the augmentation in tension or pressure. Our limited evidence suggests that at a given level of cardiac output the heart uses no more oxygen if it maintains that level of output by virtue of postextrasystolic potentiation instead of by virtue of any other means. Moreover, we have clearly shown that postextrasystolic potentiation markedly increases coronary flow over the levels seen in acute heart failure. Finally, it will be noted that we have rather meticulously limited our recommendations for clinical investigation to patients in whom death is impending and all but inevitable and in whom the risk, if any, of a slight increase in myocardial oxygen demand is one which may be assumed with absolute propriety. Of course, if one chooses to "test" this technique on patients who can derive no possible benefit from it, then one should indeed be apprehensive about the possibility of damaging a normal heart by imposing on it an abnormally high demand for oxygen. We do not feel that paired pulse stimulation or extrasystolic potentiation should be employed in humans in whom there is no intractable tachycardia or heart failure. Patients with normal or essentially normal hearts most often would not benefit from the application of this technique but could be disastrously harmed.

The second hazard lies in the risk of inducing ventricular fibrillation. Here, too, we may remark that this would be an infinitely greater catastrophe were it to occur in an essentially healthy person. In any event, we feel that it is a minimal hazard provided certain precautions are taken. We have discussed those precautions at length elsewhere,[5] and we have also discussed what we regard as the safest method of inducing postextrasystolic potentiation. We may briefly repeat: it is almost impossible to cause ventricular fibrillation with a stimulus that is only 2 or 3 msec. in duration and that exceeds the diastolic threshold by not more than a factor of two. Such a stimulus will give rise to an extrasystole that is early enough to produce a generous amount of postextrasystolic potentiation. The hazard of fibrillation increases as the stimulus is made longer and it increases as the stimulus is made stronger. The other precaution

that must be observed is that the electrodes must be isolated from ground. Either a battery stimulator or an isolation unit must be employed. The stimuli may be delivered to the myocardium through a transvenous catheter pacemaker or via transthoracic plunge electrodes inserted into the apex of the heart.[15, 20] We have some doubt as to whether relatively large electrodes (of the type used for chronic implantations) are suitable for the acute induction of postextrasystolic potentiation. To the extent that such electrodes cause temporary local injury, they will also make it difficult to evoke sufficiently early extrasystoles. That this may be so is suggested by the finding that soon after such implantations there is a marked discrepancy between the effective refractory period and the full recovery time.[21]

Finally, we may mention that if it is safe and reasonable to use paired-pulse stimulation to slow the heart then it is safe and reasonable to use postextrasystolic potentiation to strengthen the heart. This is so because postextrasystolic potentiation is usually a consequence of the use of paired pulse stimulation for slowing the heart. On the other hand, slowing the heart is not an inevitable consequence of the use of postextrasystolic potentiation, since PESP may be induced without change in the effective mechanical rate simply, as we have described elsewhere, by causing the premature stimulus to fall at the end of the relative refractory period of each beat, no matter what the rate may be. The one general reservation we should like to make is that we feel that it is improper for anyone to use this technique before becoming fully familiar with the fundamental physiological facts outlined above. Neither should it be used by persons who have not familiarized themselves with the method and its associated technical problems by studies on animals.

Summary

1) The effects of single and repetitive premature action potentials on the force of contraction of cardiac muscle (postextrasystolic potentiation) are described.

2) Paired pulse stimulation has been shown to exert a positive inotropic effect on papillary muscle, the intact *in situ* heart, the heart of the heart-lung preparation, the by-passed isovolumically contracting ventricle, and the heart in acute failure.

3) The positive inotropic effect of paired pulse stimulation has been

shown to reverse the effects of acute heart failure caused by nethalide, by constriction of the outflow tract, by the passage of time in the heart-lung preparation, by fibrillation of the ventricle and by hemorrhagic shock.

4) Various ways of inducing postextrasystolic potentiation either with or without concomitant slowing of the heart are outlined and a discussion of how the hazard of fibrillation may be avoided is given.

5) It has been suggested that maintained postextrasystolic potentiation may be suitably investigated in the clinic for certain forms of acute heart failure: failure of the heart to recover mechanical force after resuscitation; failure of the heart to recover mechanical force after cardiac surgery; failure during "irreversible" shock; and failure during shock secondary to myocardial infarction.

6) It has been shown that, by a suitable choice of rate, the phases of restitution and potentiation may be balanced so that paired pulse stimulation may be employed without an increase in contractile force.

7) It has been suggested that the use of paired pulse stimulation combined with adjustment of rate to avoid increase in cardiac output may be particularly useful when it is desirable to suppress arrhythmias without increasing the work of the heart, e.g. after a myocardial infarction in which no shock or failure has resulted but in which dangerous arrhythmias are present or likely to develop.

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